

Evaluation of Congenital and Chromosomal Anomalies Mortality in Turkey by Joinpoint Regression Analysis

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Abstract: Congenital anomalies (CAs) represents one of the main cause of fetal death, infant mortality and morbidity, and long-term disability. This study aims that it was to analyze the mortality trends of Congenital and Chromosomal Anomalies (CCAs) mortality in Turkey. This population-based observational study covers nine years in Turkey. CCAs mortality data was reported from the Turkish Statistical Institute death database by gender and age. Age-standardized mortality rates per 100,000 population were calculated by direct standardization using the WHO Reference Population. Average annual percent change (AAPC), annual percent change (APC), and 95% confidence interval (CI) were computed using the joinpoint regression analysis. Joinpoint Regression analysis results showed a significant trend for overall CCA-type mortality over the entire observation period (AAPC=3.9%, 95% CI:1.4 to 6.4). A significant increase in the mortality rate of nervous system (in male: APC:7.6%, 95% CI: 2.2 to 13.4; in female: APC:6.6%, 95% CI:2.6 to 10.7) and circulatory system (in male: APC:4.6%, 95% CI:1.5 to 7.8; in female: APC:3.4%, 95% CI:0.8 to 6.1) were observed in both gender during the study period ($p<0.001$). Congenital anomalies in Turkey are a major cause of fetal and neonatal death, however, most of the anomalies can be preventable or treatable.

Keywords: Joinpoint Regression Analysis, Chromosomal anomalies, Congenital anomalies.

INTRODUCTION

Congenital and Chromosomal Anomalies (CCAs); as known birth defects, genetic or environmental they may be of origin. Serious and difficult to treat these anomalies causing problems, especially more than once in the family when they are of genetic origin can affect the person, care, and treatment costs high, social problems in the family, to stamping, isolation, fragmentation why could it be. Postpartum treatment primary prevention of these difficult diseases. Nowadays it is the most important step. It is for the genetic factors known today good understanding and good control of environmental factors must be able to [1, 2]. Many factors may cause CCAs grouped as; unknown, multifactorial inheritance, chromosomal abnormalities, mutant genes, etiology, and environmental agents [3].

According to the 2010 GBD study results, congenital anomalies are responsible for 510 400 deaths worldwide. 1% of all deaths (6% of neonatal and postnatal infant deaths, 2.5% of deaths between the ages 1-4 years) ranks 23rd among all causes of death in the ranking [4]. When we examine the March

of Dimes (MOD) global birth defects report, 7.9 million births with severe birth defects occur each year worldwide (6% of total births). 94% of these births take place in middle and low-income countries [2]. The most serious and reliable organizations that work for the population-based epidemiological monitoring and registration of CAs in Europe (EUROCAT-European Joint Action for Congenital Anomalies and Twins) or the International Birth Defects Surveillance and Research Clearinghouse (ICBDSR) are the most serious and reliable organizations [4, 5]. The aim of the Organisation brings together research programs from around the world to investigate and prevent birth defects and lessening the impact of their consequences [1].

Studies have shown that congenital anomalies can be detected at birth or before birth. They may be in the form of a single anomaly or affect multiple organs and systems. Anomalies may occur due to genetic and non-genetic reasons such as exposure of the embryo or fetus to toxic causes. The frequency of major congenital anomalies has been reported as 3.03% in the USA and 2.39% in Europe. Among the most common teratogenic factors that cause congenital anomalies, the mother's drugs, smoking, drugs and alcohol, as well as febrile illnesses, and environmental toxic factors such as organic solvents, pesticides, heavy metals she is exposed to can be counted [5].

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It is known that the underlying cause of some structural and many functional defects detected in the baby is caused by genetic or chromosomal defects. Chromosome anomalies can be numerical or structural. It may contain one or more chromosomes (autosomes or sex chromosomes). The most common type of clinically important chromosomal abnormalities may occur with the loss or increase of chromosomes. Phenotypic effects occur or not, depending on whether structural irregularities change the genome content [6, 7].

Multifactorial inheritance; is a model of inheritance formed by the introduction of genetic factors and non-genetic factors, each of which has a relatively small effect on its own. For example, neural tube defects (NTDs) are common malformations in the newborn and are the common definition of spina bifida, anencephaly, and encephalocele malformations [8, 9].

The two most important groups of congenital anomalies; the nervous system and circulatory system anomalies. Congenital heart defects are the most common birth defect occurring at a high rate of 4-8 per 1000 live births. Since the heart and main vessels are formed in the third and eighth weeks of pregnancy, anomalies occur during these periods. Approximately 90% of congenital heart defects show multifactorial characteristics of inheritance [9]. Remaining anomalies except for congenital heart defects; it is associated with chromosome abnormalities (5-8 percent), single gene defects (3-5 percent), and teratogens (2-3 percent). An estimated 1,040,800 babies are born each year with a multifactorial congenital heart defect [2]. It has been reported that serious errors of endogenous and exogenous factors in the development of the central nervous system can cause permanent damage to the brain and spinal cord. Many children affected by neural tube defects are born with congenital defects of the brain, spine, or spinal cord, and these defects that alter the shape or function of one or more parts of the baby's body can cause lifelong disability. Spina bifida and anencephaly are the two most common forms of the neural tube [10].

Our study, based on data collected from Turkey, nervous system, and circulatory system to evaluate the two most important groups of congenital anomalies. Including data, anomalies were used to be a community-based study using temporal tendencies evaluated by joinpoint regression analysis. We can provide a better interpretation of national mortality registers for CCAs and make a comparison with the

mortality model of CCAs in other countries. Another important point in our study; Turkey reveals the importance of taking effective measures for the prevention and treatment of CCAs. Thus, the objective of this study was to analyze the CCAs mortality trend in Turkey based on sex in the period from 2009 to 2017. Thus, the objective of this study was to analyze the CCAs mortality trend in Turkey based on sex in the period from 2009 to 2017.

METHODS

Data Collection

CCAs mortality data from 2009 until 2017 were reported from the Turkish Statistical Institute death database by gender [11]. Results are presented for the following CCAs types as defined by the 10th edition of the International Classification of Diseases (ICD-10) [12]. ICD was developed by the WHO to enable international comparability for mortality statistics. Mortality rates of the nervous system (Q00-Q07), circulatory system (Q20-Q28), other (Q08-Q019 ve Q29-Q99), and all types of the CCAs (Q00-Q99) were calculated. All analyses were performed separately for males and females. Age-standardized mortality rates per 100,000 population were calculated by direct standardization using the WHO Reference Population [13]. Five-year age groups were used for the standardization.

Statistical Analysis

We investigated time trends of standardized CCAs mortality rates using joinpoint regression analysis which, is widely used in modeling time trends in mortality. Analyzes were performed using Joinpoint Regression Program [14]. The Grid Search method and Monte Carlo permutation tests were performed to identify the best-fitting combination of line segments and joinpoints. The analysis starts with a zero joinpoint and tests whether one or more joinpoints are added to the model. The model ends when there are no better joinpoints. Each breaking point in the final model represents a significant change in slope [15]. The final model shows the best fitting joinpoints where the rate changes significantly. Each joinpoint informs of a statistically significant change, APC and AAPC that are computed with are 95% confidence intervals (95%CI). AAPC is computed as a weighted average of the APCs from the joinpoint model, with the weights equal to the length of the APC interval [16]. In the analyzes, 0.05 was accepted as a significance level.

RESULTS

During the period, there were about 42,400 persons died due to CCAs (about 22,000 male and 20,000 female). Approximately 25,000 of these deaths are from the nervous system and circulatory system. The proportion of deaths due to CCAs of the nervous system (15.3%), CCAs of the circulatory system (44.6%), and CCAs of the other (40.1%).

The number of deaths and the Age-Standardized Rates (ASR) in CCAs in males and females in 2009-

2017, and is explained in (Table 1). Also, the percentage of changes in ASRs is given here. Annual age-standardized mortality rates displayed upward trends. The highest change was the nervous system with an increase of about 38% in both males and females. A similar situation was observed in the circulatory system (male 22.5%, female 21.5%). The lowest increases in ASRs was observed for others at 4% for females.

Joinpoint Regression analyzed results indicated that there was an overall significant trend for mortality of

Table 1: The Number of Deaths and Age-Standardized Death Rates for CCAs in Turkey Male and Female, 2009–2017*

	2009				2017				ASR % Changed	
	Male		Female		Male		Female		Male	Female
	Death (n)	ASR	Death (n)	ASR	Death (n)	ASR	Death (n)	ASR		
Nervous system	252	0.69	323	0.89	387	0.95	495	1.23	37.7	38.2
Circulatory system	909	2.49	740	2.05	1235	3.05	1001	2.49	22.5	21.5
Other	833	2.28	792	2.19	1075	2.65	920	2.28	16.2	4.1

*ASR: Age-Standardized Rates.

Table 2: Trends in Age-Standardized Death Rates for CCAs in Turkey According to Joinpoint Analysis. 2009–2017 (Male, Female)

		AAPC(95% CI)	Trend 1	Trend 2		
		Full Range			Period	APC (95% CI)
Male	NS	7.6 [^] (2.2;13.4) (p=0.012)	2009-2017	7.6 [^] (2.2;13.4) (p=0.012)	-	-
	CS	4.6 [^] (5.2;18.4) (p=0.010)	2009-2017	4.6 [^] (5.2;18.4) (p=0.010)	-	-
	Other	2.4 (-0.4;5.4) (p=0.091)	2009-2015	4.3 [^] (1.8;6.8) (p=0.008)	2015-2017	-3.0 (-15.8;11.8) (p=0.587)
Female	NS	6.6 [^] (2.6;10.7) (p=0.006)	2009-2017	6.6 [^] (2.6;10.7) (p=0.006)	-	-
	CS	3.4 [^] (0.8;6.1) (p=0.017)	2009-2017	3.4 [^] (0.8;6.1) (p=0.017)	-	-
	Other	1.4 (-3.6;6.6) (p=0.591)	2009-2015	3.9 (-0.4;8.5) (p=0.067)	2015-2017	-5.9 (-26.9;21.3) (p=0.543)
Total	NS	7.1 [^] (2.5;11.8) (p=0.007)	2009-2017	7.1 [^] (2.5;11.8) (p=0.007)	-	-
	CS	3.2 (-2.5;9.2) (p=0.279)	2009-2015	6.5 [^] (1.4;11.8) (p=0.023)	2015-2017	-6.0 (-29.5;25.4) (p=0.583)
	Other	1.9 (-1.9;5.9) (p=0.325)	2009-2015	4.4 [^] (0.8;7.6) (p=0.026)	2015-2017	-4.3 (-21.2;16.0) (p=0.556)
CCAs		3.9 [^] (1.4;6.4) (p=0.008)	2009-2017	3.9 [^] (1.4;6.4) (p=0.008)	-	-

*NS:Nervous System; CS:Circulatory System; AAPC: Average Annual Percent Change; CI: Confidence Interval; APC:Annual Percent Change; [^]: APC and AAPC are statistically significantly different from zero (two-sided, p < 0.05).

type of CCAs in Turkey over the entire observation period (AAPC=3.9%, 95% CI 1.4;6.4). The results of the Joinpoint Regression for both sexes are shown in (Table 2).

A significant increase in the mortality rate of the nervous system and the circulatory system was observed in both genders during the study period ($p < 0.001$, Figure 1 and Figure 2). To the comparability test, mortality trends from the Nervous System in males and females differed significantly ($p = 0.042$), mortality

trends from the circulatory system in males and females were parallel ($p = 0.196$).

When evaluated according to other types of the CCAs, two joinpoint model was obtained as the best model (Figure 3). Mortality rates of other types presented a significant increase (4.3% per year for 2009-2015) and were followed by a non-significant decrease to the end of the period (by -3.0 per year) in males.

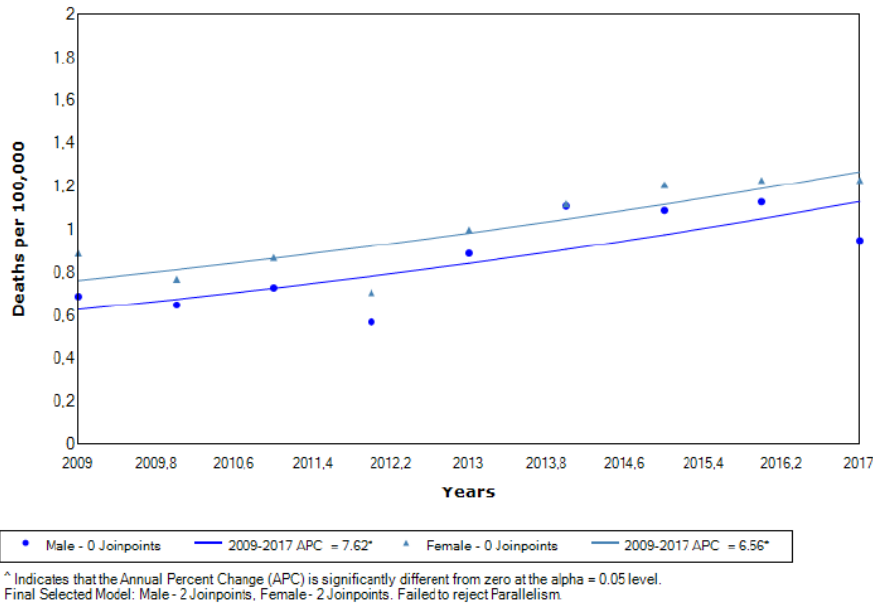


Figure 1: Observed and Modeled Age-Standardized Mortality Rates Per 100,000 Population and the ‘Best’ Joinpoint Model for the Congenital Anomalies of the Nervous System by Gender, 2009-2017.

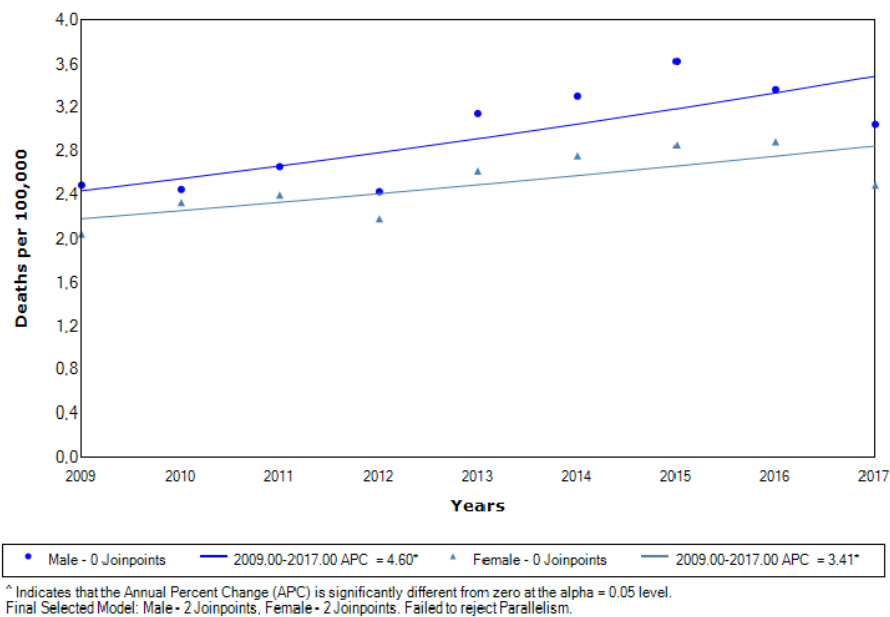


Figure 2: Observed and Modeled Age-Standardized Mortality Rates Per 100,000 Population and the ‘Best’ Joinpoint Model for the Congenital Anomalies of the Circulatory System by Gender, 2009-2017.

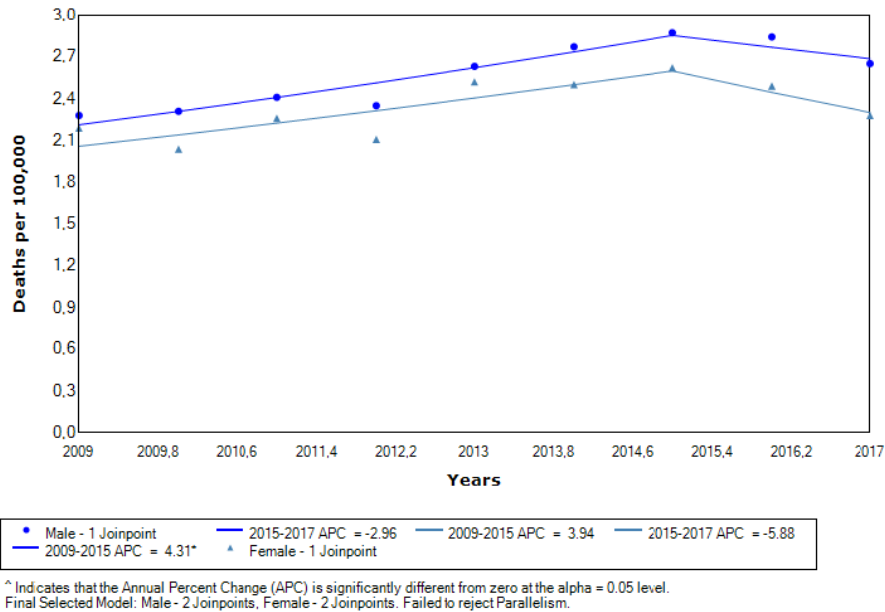


Figure 3: Observed and Modeled Age-Standardized Mortality Rates Per 100,000 Population and the ‘Best’ Joinpoint Model for the Congenital Anomalies of the Other, 2009-2017.

DISCUSSIONS

Our results show an overall unfavorable trend for CCAs mortality in Turkey over the observed between the 2009-2017 year period. During the period, there were about 42,400 persons died due to CCAs (about 22,000 male and 20,000 female). Approximately 25,000 of these deaths are from the nervous system and circulatory system. Remarkably, 56.1% of deaths caused by rarely observed CCAs occur before the age of 5 and 49.9% occur in the first year of life. This information is very important because it narrows the age at which the risk of death is highest and, consequently, maybe one of the explanatory causes of premature infant death.

According to the 2010 GBD study, the estimates were based on the WHO Mortality Database, which is considered the main data source. Modell reported that he calculated that the congenital anomaly mortality rate was predicted four times lower for the under-5 age group, suggesting that the better mortality rate predicted survival in different health systems [2, 10, 18]. Anomalies not detected at birth can be detected in 2-3% of children in the first five years, so congenital anomalies affect 4-6% of children. CA that do not cause dysfunction or aesthetic problems and can be found in approximately 15% of newborns (minor) can indicate the presence of major anomalies. Major anomalies can be found in 3% of patients with single minor anomalies, 10% of patients with two minor

anomalies, and more than 20% of patients with three or more minor anomalies. There is no etiological cause in 50-60% of major anomalies, multifactorial diseases in 20-25%, single-gene diseases in 7-8%, chromosomal disorders in 6-7%, teratogenic effects in 6%, in 1-2% the amniotic band sequence is responsible. The most common congenital anomalies, both in the world and in our country, are cardiac malformations and neural tube defects. Alonso-Ferreira V (2018) reported 13,660 deaths (53.4% male, 46.6% female) due to rare CAs in Spain during 1999-2013 [19]. In terms of CAs type, the highest percentage of death (40.3%) corresponded to rare CAs in the circulatory system, followed by 16.9% due to chromosomal abnormalities (not elsewhere classified), 14.5% due to other congenital malformations, and 9.2% due to rare CAs of the nervous system. In our country, the mortality rate due to congenital anomalies is higher than the results obtained. According to our study results, advanced maternal age, consanguineous marriage, the necessity of prenatal genetic analysis, lack of education, and social reasons can be held responsible for the increase in CAs in our country as much as in other countries. Due to the influence of different racial, ethnic, and social factors in various parts of the world, there may be differences between study results. Other explanations for these variations in the prevalence of birth defects may result from differences in study methods (*i.e.* sampling, diagnostic criteria, recording, etc.). Moreover, the accessibility and use of advanced techniques in developed countries (for example, fetal

visualization using ultrasound scanning and chromosome microarray testing at birth) have enabled the early detection of anomalies in these countries. Serious precautions should be taken to avoid congenital anomalies. For example; measures such as the prevention of consanguineous marriages, prevention of advanced age pregnancies, reaching prenatal anomalies to every pregnancy can be preventive. Because of the familial agglomeration and the increased risk of recurrence in the relatives of an affected individual, families should be referred to genetic counseling so that they can adapt to existing public health strategies [20].

High homocysteine levels were observed with decreased blood folate levels in mothers of children with NTD. This suggests that the biochemical abnormality is at the stage of transformation of tetrahydrofolate, which is required during methionine methylation of homocysteine. Since folic acid levels are highly affected by dietary intake, special attention should be paid to adding 400 micrograms of synthetic folic acid to the diet daily through supplements and/or supplements to prevent neural tube defects [21, 22]. All women should take folic acid supplements every day from the onset of pregnancy.

Previously published studies on CAs have shown that some precautions should be taken to prevent chromosomal anomalies. Placental markers, such as free fetal DNA screening in maternal blood, are reliable tests used to help predict the risk of chromosomal abnormalities or neural tube defects. Diagnostic tests such as chorionic villus sampling and amniocentesis can be used to detect high-risk pregnancies as well as diagnose chromosomal abnormalities and infections that may pass from the mother. The mother's use of substances such as alcohol, drugs, or exposure to teratogens such as thalidomide also causes congenital diseases for the baby [3]. Necessary precautions should be taken to protect the mother from these harmful substances as much as possible during pregnancy at home or work.

It should be prescribed with appropriate medication and counseling, both before and during pregnancy. Anti-epileptic drugs used for epilepsy in insulin-dependent diabetes mellitus, or sodium warfarin used for heart diseases, should be used under the supervision of a doctor during pregnancy. Infections such as syphilis and rubella cause serious birth anomalies, so the health of the mother with serious chronic diseases should be optimized and healthcare personnel should be trained on this issue [3, 23].

It is extremely important to determine the hereditary disease risk detected in previous family members, and genetic counseling and carrier screening, thus allowing couples to limit family size when there is a known risk. It is necessary to increase and strengthen the education of healthcare personnel and other people dealing with maternal and child health, and to encourage the prevention of congenital anomalies. Organizations, including patient/parent support groups, should be supported, improve patient care and prevention of birth defects by facilitating community and vocational education, and advocate for increased funding for research on the causes of birth defects [3, 24].

Strengths and Limitations of This Study

There were some restrictions in our article that forced us quite a lot. To assess the mortality-time detection more accurately, we need to acknowledge that a longer study period, but the data were not available in sufficient numbers by the time we can assess the mortality rate in Turkey. Another limitation is; we could not reach the detailed and regularly prepared CCAs data by years. In other words, due to errors in coding the causes of death, death rates resulting from CCAs could not be recorded, so enough attention might not have been given.

CONCLUSIONS

As a result, congenital anomalies such as structural malformations, metabolic disorders, and chromosomal anomalies constitute approximately one-fourth of all perinatal deaths in our countries, making it the most important cause of child death. After prematurity, the second cause of infant morbidity is that the survival of physically, mentally, and socially disabled children constitute a significant burden on health and social services. One of the easiest measures to take is the use of folic acid, which can prevent only a minority of congenital anomalies such as NTDs. Tertiary prevention (corrective surgery or medical treatment of anomalies) are surgical interventions that can be applied successfully for some malformations that will facilitate the standard of living and prolong life. This type of treatment approach; has positive effects on social life both for the affected child and for the family, as well as for the society both materially and spiritually. It is the responsibility of all physicians to have families with children affected by congenital anomalies to be referred to the relevant centers in order to ensure their correct diagnosis. In our country, it is necessary to develop recording systems that enable the monitoring

of congenital anomalies, identify common anomalies and diseases, recognize the factors that may cause them, and develop measures.

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